Remarks

Claims 52-74 are pending in the subject application. By this Amendment, Applicants have amended claims 54, 56, 59-64 and 73-74 and added new claim 76. Support for the amendments and new claim can be found throughout the subject specification and in the claims as originally filed in the PCT application (see, for example, page 8, lines 24-34). Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 52-74 are currently before the Examiner. Favorable consideration of the pending claims is respectfully requested.

Applicants gratefully acknowledge the Examiner's withdrawal of certain of the rejections under 35 U.S.C. § 112, second paragraph, and the withdrawal of the rejections under 35 U.S.C. § 112, first paragraph.

Applicants respectfully request the courtesy of an interview in this matter at the time the Examiner takes up this response for consideration.

Claims 54, 56-68, 73 and 74 are rejected under 35 U.S.C. 112, second paragraph, as indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Claims 54, 56, 59-64 and 70 recite "of interest". The claims have been amended to remove the phrase "of interest" in accordance with the Examiner's suggestion. The Office Action indicates that there is insufficient antecedent basis for the limitation "the DNA" in claim 56. By this Amendment, claim 56 has been amended to indicate that the DNA sequence recited in claim 56 refers to the DNA sequence in claim 54, subsection (c).

Claim 63 is rejected for reciting the limitation "the DNA sequence coding for a polypeptide of interest." Claim 63 has been amended to recite "DNA sequence coding for one or more polypeptides".

Claim 73 is rejected for improper antecedent basis for the phrase "said promoter domain or a functional expression promoting fragment thereof" and the Office Action indicates that claim 73 is generally unclear for its metes and bounds. Applicants have amended claim 73 in accordance with the Examiner's suggestion and believe that this issue is now moot.

Claims 52-55, 57, 58, 62-64 and 69-73 are rejected under 35 U.S.C. § 103(a) as obvious over Tuan *et al.* (U.S. Patent No. 6,395,549), Recillas-Targa *et al.* (2002), Chung *et al.* (1997) and Henderson *et al.* (U.S. Patent No. 6,432,700). Claims 52-59, 62-67, and 69-74 are rejected under 35

U.S.C. § 103(a) as obvious over Tuan *et al.* (U.S. Patent No. 6,395,549), Recillas-Targa *et al.* (2002), Chung *et al.* (1997) and Henderson *et al.* (U.S. Patent No. 6,432,700) and further in view of Perlman *et al.*(2003) and Aldrich *et al.* (1998). The Office Action indicates that Perlman *et al.* teach that CHO cells can be used to express FSH from vectors comprising the alpha and beta subunits. The Office Action states that Aldrich *et al.* teach the use of bicistronic vectors for expression, which provide for reducing the time required to develop cell pools for protein expression. Additionally, claims 52-55, 57, 58, 61-64 and 69-73 are rejected under 35 U.S.C. § 103(a) as obvious over Tuan *et al.* (U.S. Patent No. 6,395,549), Recillas-Targa *et al.* (2002), Chung *et al.* (1997) and Henderson *et al.* (U.S. Patent No. 6,432,700) and in further view of Laus *et al.* (U.S. Patent No. 6,194,152). The Office Action cites Laus *et al.* as teaching expression of thymidine kinase transgenes as a selectable marker in mammalian cells. Claims 52-59, 62-67, and 69-74 are rejected under 35 U.S.C. § 103(a) as obvious over Tuan *et al.* (U.S. Patent No. 6,395,549), Recillas-Targa *et al.* (2002), Chung *et al.* (1997) and Henderson *et al.* (U.S. Patent No. 6,432,700) and further in view of Perlman *et al.*(2003) and Aldrich *et al.* (1998). The Office Action indicates that Perlman *et al.* teach that CHO cells can be used to express FSH from vectors comprising the alpha and beta subunits. The Office Action states that Aldrich *et al.* teach the use of bicistronic vectors for expression, which provide for reducing the time required to develop cell pools for protein expression. Additionally, claims 52-55, 57, 58, 61-64 and 69-73 are rejected under 35 U.S.C. § 103(a) as obvious over Tuan *et al.* (U.S. Patent No. 6,395,549), Recillas-Targa *et al.* (2002), Chung *et al.* (1997) and Henderson *et al.* (U.S. Patent No. 6,432,700) and in further view of Laus *et al.* (U.S. Patent No. 6,194,152). The Office Action cites Laus *et al.* as teaching expression of thymidine kinase transgenes as a selectable marker in mammalian cells. Claims 52-58, 62-66, and 68-74 are rejected under 35 U.S.C. § 103(a) as obvious over Tuan *et al.* (U.S. Patent No. 6,395,549), Recillas-Targa *et al.* (2002), Chung *et al.* (1997) and Henderson *et al.* (U.S. Patent No. 6,432,700) and in further view of Anderson *et al.* (U.S. Patent No. 6,113,898) and Aldrich *et al.* (1998). The Office Action states Anderson *et al.* teach CHO cells being transformed to express the heavy and light chains of antibodies to the human B7.1 and/or B7.2 antigens. The Office Action asserts that Aldrich *et al.* teach the use of bicistronic vectors for expression, which provide for reducing the time required to develop cell pools for protein expression. Likewise, claims 52-55, 56, 57, 58, 62-66, 68-74, and 75 are rejected under 35 U.S.C. §

103(a) as obvious over Tuan *et al.* (U.S. Patent No. 6,395,549), Recillas-Targa *et al.* (2002), Chung *et al.* (1997), Henderson *et al.* (U.S. Patent No. 6,432,700), Anderson *et al.* (U.S. Patent No. 6,113,898) and Aldrich *et al.* (1998) and in further view of Adair *et al.* (U.S. Patent No. 6,632,927). Applicants respectfully assert that the claimed invention is not obvious over the cited references.

The Office Action states Tuan *et al.* teach integrating vectors comprising enhancers, insulators, and promoters to drive the expression of any gene of interest in animal cells. Further, it is taught to use barrier-function sequences to isolate the integrated vector from position effects in the chromatin to avoid silencing. Hence, Tuan *et al.* teach that it is known in the art to place barrier-function sequences on both sides of an integrating vector in order to protect it from silencing, and this can be used for the expression of desired transgenes. Further Tuan *et al.* teach the use of GFP coding sequences as a reporter for expression, and further to link the expression of such GFP to hCMV to obtain expression in cells, as it is well known that such promoters are widely active in many cell types (absent reason to believe otherwise, this is hCMV-IE1, as such is the standard utilized in the art for constitutive expression). The Office Action states that Recillas-Targa *et al.* teach that the position protection effect of the chicken beta-globin insulator is located in a larger region encompassed by Applicants' SEQ ID NO: 1, and is severable from the enhancer blocking activity. Further, it is stated that Recillas-Targa *et al.* teach that it is normal to utilize two copies of the position-effect on both sides of the vector provide for good isolation from position effects. Lastly, Recillas-Targa *et al.* teach minimization of domain sizes. The Office Action states Chung *et al.* teach that the same insulator as Recillas-Targa *et al.* is active in mammalian cells. The Office Action notes that Henderson *et al.* teach that it is optimal to minimize the size of the other components of the vector, in order to make more room for transgenes which are to be expressed. The Office Action further argues:

> Hence, from this, the Artisan would be motivated to make an integrating vector, comprising two copies of SEQ ID NO 1 on each end of the integrating vector, with the normally present base that Applicant has removed from the sequence, and further to comprise the CMV promoter driving expression of GFP. The Artisan would be so-motivated to provide the minimal sequence of the beta-globin barrier sequence of Recillas-Targa, and do so to express proteins in mammalian cells, as is taught in Chung. In addition, there is a reasonable expectation of success, as the use

of such barriers was known, the methods of minimization were known, and the methods of utilizing such to express proteins from integrated vectors was known.

However, such, in itself, does not make obvious the further deletion of the base which Applicant's SEQ ID NO: 1 is missing, from that of the known sequence of the chicken beta globin insulator/barrier sequence.

On the other hand, it is clear that the Artisan knew that the important sequences for the barrier functions were those regions that did not bind proteins (e.g., Recillas-Targa, DISCUSSION), and that intervening sequences were not known to be important. Moreover, Applicant's deleted base is within the intervening sequences (e.g., Chung, FIGURE 3, line 5 of the sequence, the penultimate "C" in such line, determined by comparison to Applicant's specification, FIGURE 1).

Hence, it would be obvious to further delete the "C" between the binding regions. The Artisan would have done so to further minimize the size the barrier region. Further the Artisan would have expected success, as such region was not bound by any proteins which cause the barrier effect.

Therefore, the Artisan would make these integrating vectors and transform mammalian cells with such vectors to express transgenes, including GFP for identification of those cells expressing the transgene. The Artisan would have expected success, as the methods were known in the Art.

The core issue in this application is whether the teachings of Henderson and Recillas-Targa *et al.* teach or suggest the desirability of deleting a single nucleotide within the sequence of the chicken beta globulin insulator. In responding to arguments presented in the last response, the Office Action argues that "[m]otivation need not be specific, as is found in the core of KSR" (see Office Action at page 12). However, the Supreme Court also stated: "it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" (KSR *Int'l Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, 1741 (2007)). Additionally, the mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the desirability of the modification (*In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992). Thus, while a person of ordinary skill in the art may possess the requisite knowledge and ability to modify the protocol, vectors and insulators taught in the individual references cited in the Office Action, the modification made to the chicken beta globulin insulator is not obvious unless the prior art suggested the desirability of the modification.

In this regard, the Office Action argues that one skilled in the art would have been motivated

or found it desirable to reduce the size of the chicken beta globulin insulator **by a single nucleotide** on the basis of the teachings of Recillas-Targa *et al.* and Henderson (Office Action at pages 11-12, emphasis added). Applicants note that Recillas-Targa *et al.* and Henderson teach the removal of large segments of nucleic acids for such a purpose (minimizing the size of various elements within a vector to increase transgene capacity). For example, Recillas-Targa *et al.* teach the removal of about 1000 bases (reducing the chicken beta globulin insulator from a size of about 1.2kb to 250bp; (see Abstract)). Henderson teaches that adenovirus vectors tolerate about 1.8 kb of additional transgene sequences if unmodified. However, the removal of large segments of the adenovirus genome allows for the insertion of larger transgene elements (see column 17, lines 13-21):

> If no adenovirus sequences have been deleted, an adenoviral vector can be packaged with extra sequences totaling up to about 5% of the genome size, or approximately 1.8 kb. If non-essential sequences are removed from the adenovirus genome, an additional 4.6 kb of insert can be tolerated (i.e., a total of about 1.8 kb plus 4.6 kb, which is about 6.4 kb). Examples of non-essential adenoviral sequences that can be deleted are E3 and E4 (as long as the E4 ORF6 is maintained).

Thus, while removal of genetic material from vectors and genetic elements within vectors would have been within the knowledge and ability of those skilled in the art, **the removal of a single nucleotide at a position within the chicken beta globulin insulator** would not have been suggested as desirable to those skilled in the art since the cited prior art would indicate that the removal of about 1000 nucleotides and/or about 3000 to 3300 nucleotides was desirable for such purposes (see Recillas-Targa *et al.*, Abstract and Henderson at column 31, lines 20-32 where the deletion of between 3000 and 3300 bases in adenovirus vectors is discussed). Applicants further note that modification of the chicken beta globulin insulator as taught by Recillas-Targa *et al* would have resulted in freeing about 4 kb of space within a vector containing two insulators on each side of a transgene element. One skilled in the art would not have been motivated to remove a single nucleotide within the insulator taught by Recillas-Targa *et al.* (*i.e.*, one skilled in the art would not have been motivated to free an additional 4 bases of space by deleting a nucleotide within an insulator element that already freed 4kb of space), particularly since those skilled in the art deleted entire segments of adenovirus vector genomes in order to increase transgene capacity (see, for example, Gorziglia *et al.* (J. Virol., 1999, 73:6048-6055, page 6050, column 2, last full paragraph

discussing deletion of 3.7kb, 6.5kb segments from the adenovirus genome and Henderson discussing deletion of 3-3.3kb segments of the adenovirus genome for the purposes o increasing transgene capacity). Indeed, the state of the art, as evidenced by Henderson and Gorziglia *et al.* indicate that those skilled in the art recognized that the deletion of kilobase segments of nucleic acids, not single nucleotides, was how one increased the capacity of a vector for a transgene and there is not motivation or indication that one skilled in the art would have been motivated to delete a single nucleotide for such a purpose. Accordingly, it is submitted that one of ordinary skill in the art would not have been motivated to undertake the deletion of a single nucleotide within the chicken beta globulin gene as has been argued by the Patent Office. Thus, the claimed invention would not have been obvious in view of the combined teachings of the references and reconsideration and withdrawal of the rejection of record is respectfully requested.

It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position. Applicants expressly reserve the right to pursue the invention(s) disclosed in the subject application, including any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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